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# DOCUMENT:

# Selection of Endpoints for Determining EARs/AIs and ULs

**Developed by:**
**Margaret Cheney, PhD**
**Health Canada (retired)**
**Ottawa, Ontario, Canada**

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**Dr. Margaret Cheney**
**Health Canada (retired)**

## 1 Introduction

The establishment of the Dietary Reference Intakes required the selection of appropriate endpoints on which to base the Estimated Average Requirement (EAR), the Adequate Intake (AI) and the Tolerable Upper Intake Level (UL). In reviewing the 69 nutrients included in the DRI Reports, the Nutrient Panels considered some 400 endpoints.

The endpoint is inherent in the definition of the EAR: the daily intake value that is estimated to meet the requirement, **as defined by the specified indicator or criterion of adequacy**, in 50 per cent of the apparently healthy individuals in a life stage or gender group. (emphasis added) Adequacy could range from preventing overt deficiency to maintaining a biochemical function, maintaining stores or reducing risk of a chronic disease.

The AI is defined as a value based on experimentally derived intake levels or approximations of observed mean nutrient intakes by a group(s) of healthy people. Endpoints for AIs differ from those for EARs by including values based on intakes.

The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the specified life stage group. Endpoints for the critical adverse effect range from biochemical to clinical effects and differ in severity and their time course.

The current conceptual framework for DRI development does not provide general criteria to guide the selection of the indicator to use in determining the EAR or AI. The choice has been based on the scientific judgement of the various nutrient panels (IOM 1997). The panels considered a broad range of endpoints for each nutrient. These were listed in each nutrient chapter of the DRI reports and a rationale for the acceptance or rejection of each endpoint was given. It is obvious that the choice of endpoint has a significant impact on the reference value. This was illustrated for vitamin A by Yates (2007). The indicator of adequacy selected was adequate liver

stores which resulted in an EAR for men of 625 μg RAE/day. Had dark adaptation been chosen as the endpoint, the EAR would have been 300 μg RAE/day.

This paper considers the endpoints with a view to highlighting some issues which may be relevant to any future development of guidance on the selection of endpoints for future DRIs. As an exercise, this paper attempts to classify the endpoints selected to determine EARs/AIs and ULs in order to examine the consistency of endpoints across nutrients in terms of their impact on health . It also looks at the result of the decision to include reduction in risk of chronic disease as an endpoint on the establishment of the DRIs.

# 2 Classification of Endpoints

## *2.1 Existing Categorizations for Endpoints Related to Nutrients*

### 2.1.1 Categories of Endpoints Used for Indicator of Adequacy

At one time, endpoints could be categorized as clinical or biochemical, however, the advent of more advanced and complex analytical procedures has expanded the number of endpoints, resulted in more endpoints termed "functional" and blurred the lines between clinical and functional categories. The FAO/WHO Expert Consultation on vitamin and mineral requirements (FAO/WHO 1998) divided endpoints into the following categories: clinical endpoints, nutrient balance, functional endpoints, reduction of risk of chronic disease or developmental disorders, and customary intakes. Table 1 is an adaptation of this classification which also includes a category of biochemical endpoints for nutrient levels in blood, urine and tissues.

Table 1 Categories of Endpoints for Adequacy

| |
|---|
| Clinical:<br>physical signs of deficiency disease; reductions in ponderal and linear growth rates; altered body composition; compromised host defense systems; impairment of gastrointestinal or immune function; abnormal cognitive performance/neurological impairment; increased susceptibility to disease; increased morbidity |

| |
|---|
| Nutrient Balance/ Factorial model |
| Biochemical:<br>Nutrient levels in blood and tissues; nutrient excretion; tissue retention; nutrient stores or critical tissue pools |
| Functional:<br>Neurodevelopment; bone health; substrate concentrations; enzyme concentration and activity; hormone levels; indices of anabolic and catabolic activity (e.g. metabolites); immune function; antioxidant activity; body composition; gene expression |
| Risk of chronic disease |
| Risk of developmental abnormalities |
| Customary intakes of healthy populations |

### 2.1.2 Categories of Endpoints Used for Excess

The report of the Joint FAO/WHO Technical Workshop on Food Nutrient Risk Assessment (2005) included classification of endpoints for nutrient substances. The classification[01] indicated measurable effects of high levels of intake within the causal pathway of an adverse health effect. These effects can range from biochemical changes without functional significance to clinical signs that signify irreversible impairment of organ function. The classification is shown in Table 2.

**Table 2: Sequence of observable effects in increasing order of severity of health impact**

| |
|---|
| 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae |
| 2. Biochemical changes outside the homeostatic range and without known sequelae |
| 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |

4. Clinical symptoms indicative of a minor but reversible change

5. Clinical signs indicative of a minor but reversible change

6. Clinical signs indicative of significant but reversible effects

7. Clinical signs indicative of significant but reversible organ or tissue damage

8. Clinical signs indicative of irreversible organ or tissue damage

Adapted from Renwick et al., 2004 and FAO/WHO 2005
NOTES: For our use, we will define **SIGN** as *'Any objective evidence or manifestation of an illness or disordered function of the body. Signs are apparent to observers, as opposed to symptoms, which may be obvious only to the patient.'* **SYMPTOM** will be defined as *'Any change in the body or its functions, as perceived by the patient. A symptom represents the subjective experience of disease. Symptoms are described by patients in their complaint or history of the present illness. By contrast, signs are the objective findings observed by health care providers during the examination of patients'* (SOURCE: Taber's Cyclopedic Medical Dictionary [www.tabers.com]).

## *2.2 Exercise: Classification of DRI Endpoints*

Because of its simplicity and because of its possible potential to be equally applicable to endpoints for adequacy (EARs/AIs) and endpoints for excess (ULs), the table developed by Renwick (2004), was modified to include reference to adverse health effects due to deficiency as well as excess. The table was used as a tool to classify the endpoints in order to assess their variability according to their impact on health in terms of the severity or nature of the observable effect. This use of the table for classification of endpoints is not related in any way to other potential uses that might be made of the table such as, for example, the selection of endpoints.

### 2.2.1 Classification of Indicators of Adequacy

As shown in Table 3, the endpoints chosen as indicators of adequacy by the DRI nutrient panels have been classified as to category and as to the severity or nature) of the observable effect. The sequence of nutrients in the table is based on the individual DRI reports

in chronological order. The DRI process evolved as it progressed and different experts were involved in the nutrient panels. Listing the nutrients in alphabetical order disregards the evolutionary nature of the review process and mixes up the expert panels. [O2]

The endpoints for the EARs were all based on the results of biochemical and clinical studies. They fell into four main categories: nutrient balance, factorial modeling, nutrient and nutrient metabolite levels in blood and urine, and functional measures such as enzyme concentrations and measures of antioxidant activity.

The endpoints for the AI covered a broader range of categories. They included balance studies, serum nutrient levels, functional measures such as bone mineral density and fractures, chronic disease prevention, and intakes. The indicators of adequacy based on intakes included observed intakes of apparently healthy populations (NHANES and CSF), intakes determined from the FDA Total Diet Study, intakes based on designed diets and extrapolation from human milk intakes.

The classification system based on severity or nature of the observable effect was not completely satisfactory for the purposes of this exercise and would require further modification and development to distinguish between the endpoints to demonstrate variability. Nutrient balance was arbitrarily classified as level 1 – changes within the homeostatic range – because balance studies attempt to achieve zero balance. Depletion/repletion studies were classified as level 3 because depletion can result in changes outside the homeostatic range with adverse effects. It was assumed that functional changes such as enzyme levels and activity were outside the homeostatic range therefore they were also classified as level 3. As a result, most biochemical and functional endpoints were classified at the same level (3), thus it was not possible with this classification system to distinguish among these endpoints on the basis of severity. Furthermore, because the biochemical and functional endpoints begin as changes from the norm at levels 1 (change within homeostatic range) and 2 (change outside homeostatic range without known adverse sequelae), it is not certain whether they should be classified as a continuum of change as is the case with some clinical endpoints.

**TABLE 3:** Indicators of Adequacy for EAR or AI: Category of Endpoint and Classification of Observable Effects

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Calcium | AI | **Calcium balance, BMD, factorial approach** | Nutrient balance + factorial model; Functional | 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae<br>3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| | | **Calcium retention –desirable rates as determined by Ca balance studies, factorial estimates of requirements, BMD and BMC** | Nutrient balance + factorial model; Functional: bone health; tissue retention | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Phosphorus | EAR | **Accretion and factorial approach (children and adolescents)** | Factorial model | |
| | | **Serum $P_i$ (adults and adolescents)** | Biochemical: nutrient levels in serum | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Magnesium | EAR | **Magnesium balance studies (ages 1 -70 yrs )** | Nutrient balance | 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae |
| | | **Intracellular studies; decreases in absorption (>70 yrs)** | Biochemical: nutrient levels | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Vitamin D | AI | **Serum 25(OH)D (older infants, children, adolescents, adults)** | Biochemical: nutrient levels in serum | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| | | **Evaluation of skeletal health (infants < 6 mos: linear growth and bone mass, prevention of rickets; adults >50 to 70 yrs: bone loss (BMD, BMC); adults >70 yrs: bone loss (BMD, BMC), fractures, parathyroid hormone)** | Clinical: reduction in linear growth rate; increased morbidity<br><br>Functional: bone health | 8. Clinical signs indicative of irreversible organ or tissue damage |
| Fluoride | AI | **Prevention of Dental Caries** | Clinical: increased susceptibility to disease | 8. Clinical signs indicative of irreversible organ or tissue damage |
| Thiamin | EAR | **Urinary thiamin excretion (all age groups except infants, extrapolation from young adult males)** | Biochemical: nutrient excretion | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| | | **Erythrocyte transketolase activity** | Functional: enzyme activity | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Riboflavin | EAR | **Concurrent analyses (erythrocyte glutathione reductase activity coefficient; urinary excretion, erythrocyte flavin,) (all age groups except infants, children extrapolated from adults)** | Biochemical and functional | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Niacin | EAR | **Urinary excretion of $N^1$-methylnicotinamide and its 2-pyridone derivative $N^1$-methyl-2-pyridone-5-carboxamide** | Biochemical: excretion of nutrient metabolites | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Vitamin $B_6$ | EAR | **Concurrent analyses (plasma PLP, urinary pyridoxic acid, tryptophan metabolites, α-EAST, α-EALT) (children and adolescents except infants extrapolated from adults)** | Biochemical and functional | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Folate | EAR | **Combination of erythrocyte folate, serum or plasma folate and plasma homocsyteine (children and adolescents except infants extrapolated from adults** | Biochemical and functional | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Vitamin $B_{12}$ | EAR | **Indicators of hematological response (stable hemoglobin value, normal MCV, normal reticulocyte response) (primary criterion)** | Functional: abnormal hematological response | 6. Clinical signs indicative of significant but reversible effects |
| | | **Serum and plasma vitamin $B_{12}$** | Biochemical: nutrient level in plasma | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Pantothenic Acid | AI | **Pantothenic acid intakes – midpt of range of intakes; small groups of adults and adolescents** | | |
| Biotin | AI | **Biotin intake of infants fed exclusively on human milk** | | |
| Choline | AI | **Markers of liver dysfunction** | Functional: organ dysfunction | 6. Clinical signs indicative of significant but reversible effects |
| Vitamin C | EAR | **Antioxidant functions in leukocytes (Near maximal neutrophil concentration with minimal urinary excretion ascorbate)** | Functional: antioxidant activity<br>Biochemical: nutrient levels in blood; tissue retention | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Vitamin E | EAR | **Plasma α-tocopherol concentration** | Biochemical: nutrient level in plasma | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| | | **Hydrogen peroxide-induced hemolysis** | Functional: antioxidant activity | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Selenium | EAR | **Glutathione peroxidases and selenoprotein P in blood (levels to achieve plateau concentrations of plasma selenoproteins/)** | Functional: enzyme concentrations; biochemical: nutrient levels | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| β-Carotene & other Carotenoids | --- | | | |
| Vitamin A | EAR | **Amount dietary vitamin A required to maintain a given body-pool size in well-nourished adults** | Factorial model to achieve given level of stores | |
| Vitamin K | AI | **Highest median Vitamin K intakes NHANESIII (adults, children and adolescents except infants)** | Customary intake of healthy population | |
| Chromium | AI | **Chromium content per 1000 kcal in well-balanced designed adult diets times the highest energy intakes for adults and extrapolated to children and adolescents** | | |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Copper | EAR | **Combination of ceruloplasmin concentration, erythrocyte superoxide dismutase activity, platelet copper concentration and cytochrome c oxidase activity, plasma copper concentration and factorial analysis** | Functional and biochemical. Factorial model | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Iodine | EAR | **Iodine accumulation and turnover** | Biochemical: tissue retention | 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae |
| | | **Iodine balance** | Nutrient balance | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Iron | EAR | **Indicator of adequacy – normal functional iron concentration with only minimal stores (serum ferritin 15 µg/L) calculated by factorial modeling because distribution of iron requirements is skewed.** | Factorial model to achieve given level of stores | |
| Manganese | AI | **Median intake levels from FDA Total Diet Study** | | |
| Molybdenum | EAR | **Molybdenum balance** | Nutrient balance | 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Zinc | EAR | **Minimal quantity of absorbed zinc required to match the total excretion of endogenous zinc plus growth where appropriate calculated using the factorial method adjusted for fractional absorption (older infants, children, adolescents, adults)** | Factorial model | |
| | | **Physical growth response to zinc supplementation (used to check EAR derived by factorial method in older infants and young children 7 mos – 3 yrs)** | Clinical: reductions in linear growth rates | 6. Clinical signs indicative of significant but reversible effects |
| Dietary Carbohydrates | EAR | **Glucose utilization by the brain** | Functional: substrate | 3. Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess |
| Total Fiber | AI | **Prevention of CHD** | Risk of chronic disease | 8. Clinical signs indicative of irreversible organ or tissue damage |
| n-6 PUFA | AI | **Median intakes US population CSFII** | Customary intakes of healthy populations | |
| n-3 PUFA | AI | **Median intakes US population CSFII** | Customary intakes of healthy populations | |
| Protein & Amino Acids | EAR | **N Balance (> 18 yrs)** | Nutrient balance | 1. Biochemical changes within the homeostatic range and without indication of adverse sequelae |
| | | **N Balance + protein deposition ( 7 mos – 18 yrs)** Factorial method | Factorial model | |
| Water | AI | **AI based on median intakes of total water NHANES III** | Customary intakes of healthy populations | |

| Nutrient | Ref Value | Indicators considered in estimating requirements | Category of Endpoint | Classification of Observable Effect [number indicates level in Table 2] |
|---|---|---|---|---|
| Potassium | AI | **Intake level to lower blood pressure, to reduce the extent of salt sensitivity and to minimize risk of kidney stones (children and adolescents extrapolated from adults using average energy intake)** | Risk of chronic disease | |
| Sodium | AI | **Amount based on meeting the sodium needs of moderately active apparently healthy individuals in a temperate climate as well as those of other important nutrients using foods found in a western-type diet (children and adolescents extrapolated from adults using relative energy intakes)** | | |
| Chloride | AI | Equimolar with sodium | | --- |
| Sulfate | - | Requirements met by requirements for sulfur amino acids | | --- |

### 2.2.1 Classification of Indicators of Excess

The endpoints on which the ULs were based were classified according to the severity or nature of the observable effects. The results are shown in Table 4. The classification system worked better for adverse effects than for indicators of adequacy in demonstrating variability of health impact due to the greater number and range of clinical endpoints. The clinical adverse effects varied from acute reversible symptoms to signs of irreversible organ and tissue damage. Five critical adverse effects were biochemical changes.

**Table 4:** Endpoints for UL: Classification of Observable Effects

| Nutrient | Critical Adverse Effect | Classification [number indicates level in Table 2] |
|---|---|---|
| Calcium | **Hypercalcemia and renal insufficiency (Milk Alkali Syndrome)** | (6) Clinical signs indicative of significant but reversible effects |
| Phosphorus | **Hyperphosphatemia** leading to risk of<br>- adjustments in calcium-regulating hormones (PTH)<br>- metastatic calcification of soft tissues<br>- skeletal porosity<br>- interference with calcium absorption | (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to excess |
| Magnesium | **Diarrhea (applies to nonfood sources of magnesium only)** | (4) Clinical symptoms indicative of a minor but reversible change |
| Vitamin D | **Hypercalcemia of hypervitaminosis D** | (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to excess |
| Fluoride | **Adverse cosmetic effect: enamel fluorosis (infants and children 0 to 8 yrs)**<br>**Adverse functional effect: skeletal fluorosis (all age groups > 8yrs)** | (5) Clinical sign indicative of a minor but irreversible change<br>(6-8) Clinical signs indicative of significant but reversible effects - Clinical signs indicative of significant but reversible organ or tissue damage - Clinical signs indicative of irreversible organ or tissue damage |
| Niacin | **Vasodilatory effects (flushing) applies only to nicotinic acid and nicotinamide as supplements, food fortificants or pharmacologic agents** | (6) Clinical signs indicative of significant but reversible effects |

| | | |
|---|---|---|
| Vitamin $B_6$ | **Sensory neuropathy** | (7-8) Clinical signs indicative of significant but reversible organ or tissue damage - Clinical signs indicative of irreversible organ or tissue damage |
| Folate | **Neurological effects of supplemental folate in individuals with vitamin $B_{12}$ deficiency** | (7 - 8) Clinical signs indicative of significant but reversible organ or tissue damage - Clinical signs indicative of irreversible organ or tissue damage |
| Choline | **Body odor, sweating and salivation (fishy body odor, vomiting, GI effects)** | (4) Clinical symptoms indicative of a minor change but reversible change Secondary indicator |
| | **Hypotension (primary indicator)** | (5) Clinical sign indicative of a minor change but reversible change |
| Vitamin C | **Gastrointestinal effects (nausea, abdominal cramps, diarrhea)** | (4) Clinical symptoms indicative of a minor change but reversible change |
| Vitamin E | **Hemorrhagic toxicity in experimental animals** | (8) Clinical signs indicative of irreversible organ damage (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to either deficiency or excess (e.g.,, increased prothrombin time, interference with blood coagulation) |
| Selenium | **Chronic selenosis (hair and nail brittleness and loss**; other symptoms: GI disturbance, skin rash, garlic breath odor, fatigue, irritability, nervous system abnormalities) | (7) Clinical signs indicative of significant but reversible tissue damage |
| Vitamin A | **Teratogenicity (basis for UL in women of child -bearing age)** | (8) Clinical signs indicative of irreversible organ and tissue damage |
| | **Liver abnormalities (reversibly elevated liver enzyme activity → widespread fibrosis and cirrhosis → sometimes death)** | (5-8) Clinical symptoms of significant but reversible effects - Clinical signs indicative of irreversible organ damage |

| | | |
|---|---|---|
| | **Adverse effects in infants and children** (intracranial (bulging fontanel) and skeletal abnormalities, bone tenderness and pain, increased intracranial pressure, desquamation, brittle nails, mouth fissures, alopecia, fever, headache, lethargy, irritability, weight loss, vomiting and hepatomegaly) | (7) Clinical signs indicative of significant but reversible organ damage, reversible tissue damage |
| Copper | **Liver damage** | (7 - 8) Clinical signs indicative of significant but reversible organ damage - Clinical signs indicative of irreversible organ damage |
| Iodine | Hypothyroidism, **elevated thyroid stimulating hormone** | (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to excess |
| Iron | **Gastrointestinal effects** (constipation, nausea, vomiting, diarrhea) | (4 - 5) Clinical symptoms and signs of significant but reversible effects |
| Manganese | **Elevated blood manganese and neurotoxicity** | (7 - 8) Clinical signs indicative of significant but reversible organ and/or tissue damage - Clinical signs indicative of irreversible organ and/or tissue damage |
| Molybdenum | **Reproductive effects in rats and mice (Rats: prolonged estrus cycle, decreased gestational weight gain in pups, adverse effects on embryogenesis; mice: early deaths of offspring, dead litters, maternal deaths and failure to breed)** | (7 - 8) Clinical signs indicative of significant but reversible organ and tissue damage - Clinical signs indicative of irreversible organ and tissue damage |
| Zinc | **Reduced copper status** | (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to excess |
| | **Serum copper and cholesterol concentrations in infants** | (3) Biochemical changes outside homeostatic range which represent a biomarker of potential adverse effects due to excess |
| Boron | **Reproductive and developmental effects in animals (Rats, dogs and mice: adverse effects in the testes and on male fertility)** | (7 - 8) Clinical signs indicative of significant but reversible organ and tissue damage - Clinical signs indicative of irreversible organ and tissue damage |

| | | |
|---|---|---|
| Nickel | *UL applies to excess nickel intake as soluble nickel salt*<br>**Subchronic and chronic effects in animals** increased mortality<br>- **clinical signs of general systemic toxicity**<br>- **decreased body weight gains** | (7 - 8) Clinical signs indicative of significant but reversible organ and tissue damage - Clinical signs indicative of irreversible organ and tissue damage |
| Vanadium | *UL applies to total vanadium from food, water and supplements*<br>**Renal toxicity**<br>(**Rats: histopathological lesions and increased urea, uric acid and creatine, decreased weight gain; mice: acute tubular necrosis)** | (7 - 8) Clinical signs indicative of significant but reversible organ and tissue damage - Clinical signs indicative of irreversible organ and tissue damage |
| Sodium | **Blood pressure** | (6) Clinical signs indicative of significant but reversible effects<br>(7) Clinical signs indicative of significant but reversible organ or tissue damage<br>(8) Clinical signs indicative of irreversible organ or tissue damage |
| Chloride | Equimolar to sodium | |

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# 3 Endpoint: Reduction in Risk of Chronic Disease

During the consultations leading up to the development of the DRIs, the Food and Nutrition Board concluded that "reduction in risk of chronic disease is a concept that should be included in the formulation of future RDAs where sufficient data for efficacy and safety exist". (IOM 1994)

The assessment of the strength of the data supporting a nutrient's role in decreasing the risk of chronic disease was based on the following criteria (IOM 1997, Hill 1971):

- Strength of association, usually expressed as relative risk;
- Dose-response relationship;
- Temporally correct association, with exposure preceding onset of disease;
- Consistency of association;
- Specificity of association; and biological plausibility.

As shown in Table 5, reducing risk of chronic disease was considered as an endpoint for nineteen nutrients, however, the evidence was not considered sufficient to establish a

dietary reference intake except in the case of three nutrients: dietary fibre (reduced risk of coronary heart disease); potassium (reduced risk of hypertension and kidney stones) and fluoride (prevention of dental caries). It was considered that there was insufficient evidence to establish an EAR for any of these nutrients and an AI was set.

Table5: DRIs and Reduction of Risk of Chronic Disease

| **Chronic Diseases considered as Endpoints** | **Nutrients** | **Nutrient with sufficient evidence for DRI** | **Ref Value** |
|---|---|---|---|
| Osteoporosis | Calcium, Magnesium, Vitamin D, Vitamin K | | |
| Cancer colorectal, esophageal, lung, stomach, cervical, breast, pancreatic, oral cavity, larynx, pharynx, endometrial, ovarian | Calcium, Riboflavin, Folate, vitamin C, vitamin E, β-carotene, total fiber | | |
| Hypertension | Calcium, magnesium, Sodium, potassium | Potassium | AI Ages > 1 yr |
| Cardiovascular disease (myocardial infarction, coronary heart disease, hyperlipidemia, atherosclerosis) | Magnesium, vitamin $B_6$, Choline, vitamin C, vitamin E, β-carotene, vitamin K, total fiber | Total Fiber (coronary heart disease) | AI Ages > 1 yr |
| Diabetes mellitus (insulin resistance, impaired glucose tolerance) | Magnesium, vitamin E, chromium, total fiber, sodium | | |
| Dental caries | Fluoride | Fluoride | AI Ages > 6 mos |
| Cataracts/ Macular degeneration | Riboflavin, vitamin C, vitamin E, β-carotene, | | |
| Cognitive functions, dementia, memory | vitamin $B_6$, folate, choline, vitamin C, vitamin E | | |
| Asthma and obstructive pulmonary disease | Vitamin C | | |
| Immune function | Vitamin E, β-carotene, vitamin A | | |
| Kidney stones | Potassium | Potassium | AI Ages>1 yr |

# 4 Discussion and Conclusions

As noted, there are no criteria specified within the current DRI development framework to guide the various nutrient panels in the selection of endpoints. The classification of endpoints illustrated the variability across the nutrients in terms of health impact. Although the limitations of the available data have considerable potential to interfere with a goal of consistency, it would be desirable to achieve some conceptual consistency in the selection of endpoints.

The lack of consistency was particularly evident in the case of endpoints for the AI and the UL. The selection of endpoints for upper levels of intake was constrained by a lack of data in most cases and should improve as more data become available. In the case of the endpoints for adequacy, ranking the endpoints according to sensitivity and health impact might have contributed to greater consistency in their selection.

Both apparent dietary adequacy based on observed intakes and nutritional health based on clinical/biochemical measures were used as endpoints to set the AIs. The meanings of dietary adequacy and nutritional health should be the same otherwise there are two different classes of reference values with the same name (AI). It is important that both can be interpreted in relation to public health and policy applications.

Although the relationship with chronic disease prevention was examined in depth, the data were considered sufficient for only three nutrients and only for setting AIs. This raises the question of the viability of using chronic disease prevention as an appropriate endpoint for the current DRI model, as it is now defined. One problem is specificity. Osteoporotic fractures cannot be considered a specific endpoint for calcium deficiency in the way that rachitic bone changes are a specific endpoint for vitamin D deficiency. Continued interest in chronic disease endpoints may require modified or different approaches to the framework for DRI development.

Development of guidance for selecting endpoints could be an important next step because it will increase the likelihood that the approach used by future nutrient panels would be consistent, and transparent. The basis for the selection of endpoints would need to be specified and would need to be tied to the purposes of the DRI values for both adequacy and excess.

Choice of endpoints for the definition of nutrient requirements must reflect the purpose and application of the process of estimating nutrient requirements (requirements for what?). A commonly articulated basis for selecting an endpoint is that it provides "public health protection." The questions that follows are: "what level of public health protection?"; "is that a realistic goal?".

[c3]While the most pragmatic and perhaps most commonly practiced approach has been to use an endpoint for which there is a considerable amount of data, the selection of an endpoint because it has been well studied may well not be consistent with the use of an endpoint matched to the purpose of the DRI values. This paper points to the need for

further study and discussion of the selection of endpoints given their integral role in the determination of requirements.

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